REMARKS

Claims 1-6 have been canceled. Claims 7-18 are currently under examination.

In the January 25th communication, the Examiner indicated that all rejections have been withdrawn except the rejections under 35 U.S.C. §112 and the obvious-type double-patenting rejection in view of U.S. Patent 6,872,399. In view of the following, reconsideration of such rejections is respectfully requested.

Section 112 Rejection

Claims 7-18 have been rejected under 35 U.S.C. §112, first paragraph for allegedly failing to comply with the enablement requirement. According to the Office Action, the specification does not set forth enablement of a vaccine comprising 4 or more inactivated dermatophyte strains.

Applicants respectfully disagree. "When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement". *In re Wright*, 27 U.S.P.Q. 1510, 1513 (Fed. Cir. 1993) (emphasis added). See also *In re Morehouse*, U.S.P.Q. 29, 32 (CCPA 1976).

Upon careful review of the previous Office Action dated January 25, 2006, no proper explanation or sufficient reasons were given by the Examiner as to why the scope of protection provided by the claims is allegedly not enabled by the specification. In fact the Examiner has already agreed that the specification is enabling for the use of the inactivated strain in a vaccine composition:

> "Claim 18, 21-23, 34 and 38-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for use of the inactivated strain**, does not reasonably provide enablement for one antigen from the dermatophytes, T. verrucosum, to be used in the vaccine

> composition." (Final Office Action dated August 29, 2001 for related application 09/256,915, to which benefit is claimed in the subject application, page 3 at 6) (emphasis added).

Similarly, the Examiner has stated:

> Applicants have asserted that the immunogenic response produced by immunization of an animal with a vaccine comprising a single inactivated strain, as described in Table 1-7 establishes (results) in immunity to that strain. The Examiner agrees that administration of **a single inactivated strain establishes immunity**, however an immune response does not establish vaccine protection against dermatomycosis as presently claimed by Applicants. (Office Action at page 5, second paragraph) (emphasis added).

Applicants fully agree with Examiner's conclusion that the specification is fully enabling for the use of any of the inactivated strains. Accordingly, if the use of a vaccine containing only one inactivated strain is considered to be disclosed in an enabling manner, how can the use of a vaccine containing four, five, six, seven or eight of such strains not be considered to be disclosed in an enabling manner? In short, if a vaccine comprising one strain is shown to provide immunity and to comply with the requirements of 35 U.S.C. 112, first paragraph, why should a vaccine comprising several of said strains not provide immunity? If the Examiner's concerns are based on the recitation of vaccine, please see the comments beginning on page 14 below.

The Examiner put forward several, unsupported allegations as discussed below:

(a) "It is not clear what Applicants used in the vaccine composition. Example 1, page 18 indicates that "[A]fter 2 days, 125 ml of each culture in suspension is taken and mixed in a single container. The vaccine may be prepared by mixing together various combinations of the given strains." Exactly what was the composition of the vaccine administered that gave the results found in Tables 9 and 10? It is not clear if all 8 dermatophytes were used or some combinations of 3, 4, 6 or 7 dermatophytes. It is not clear that the specific combination of 3 dermatophytes as set forth in claim 2 were used." (Office Action at page 3, first paragraph).

(b) "Specifically, the specification has not taught how to use the claimed vaccine. Mixing each culture in a single container or mixing together various combinations of the given cultures is set forth. However, it is not clear which composition (all 8 cultures in one container or various combinations of less than 8 cultures and if less than 8 cultures specifically which ones) was used to generate the data found on tables 9 and 10 of the specification." (Office Action at page 3, second paragraph).

(c) "Does Applicant intend for "immunogenic response" to mean that vaccine protection has been established, see page 11, or "establishing immunity" to mean vaccine protection has been established, see Tables 1-7?" (Office Action at page 3, first paragraph). The Examiner further cites Gudding et al (Can. Vet. J. 1995) and continues "Further, the inactivated vaccine against ringworm must be capable of eliciting both humoral and cellular immune responses, of which the cellular immune response is crucial for protection and adjuvants are important in stimulating the cellular branch of the immune system (pp. 303-304). In view of the state of the art it is not clear if protection has been established against ringworm infection when Applicants state (see tables 1-7) "establishes immunity". It is not clear what type of immunity is established. Applicant's vaccine composition does not recite a carrier or adjuvant, however Gudding indicates that the adjuvants are important in stimulating the cellular branch of the immune system and the cellular branch is crucial for protection. (Office Action at page 4, second paragraph)

Allegation (a)

With regard to allegation (a), the Examiner has cited only part of Example 1. Omitted is the preceding paragraph:

> "To produce 1 liter of vaccine, cultures are taken of the strains VKPGF-931/410, 930/1032, 929/381, 551/68, 928/1393, 727/1311, 728/120, and 729/59 and grown in agar/wort at 26°C for 15 days. Each culture is grown

> in 8 mattress flasks. The fungal mass is then lifted off, homogenized, placed in 200 ml of solution and added to each mixer. The solution used is an aqueous solution containing 1% fermented hydrolyzed muscle protein, 10% glucose and 1% yeast extract. The concentration of microconidia is brought to 90 million per ml of homogenate. After 2 days, 125 ml of <u>each culture</u> in suspension is taken and mixed in a single container." (emphasis added)

Therefore, from the quoted wording, it is clear to the skilled person that in cited Example 1 the 8-fold vaccine, as covered by claim 7, was prepared and used in prophylaxis and therapy.

The sentence "The vaccine <u>may</u> be prepared by mixing together various combinations of the given strains" (emphasis added), uses the term "may" which clearly indicates to the skilled person what optionally <u>may be</u> done, e.g. instead of eight strains, the combination of four, five, six, and seven strains as recited in claims 7-18 may be used in a vaccine according to the invention.

Allegation (b)

Regarding allegation (b), the wording of Example 1 clearly states that each of the eight cultures is first cultured separately and homogenized:

> "<u>Each culture</u> is grown in 8 mattress flasks. The fungal mass is then lifted off, homogenized, placed in 200 ml of solution and added to each mixer."

and <u>then</u> combined into one container:

> "After 2 days, 125 ml of <u>each culture</u> in suspension is taken and mixed in a single container."

Further, the specification extensively describes immunizing the animals using the vaccine prepared in Example 1 to determine dosage to be given and the method of administration for prevention and treatment in ten different animal families (page 18, line 33 and Table 8). The effectiveness of the vaccine in preventing disease in 24 animal species is given (Example 2, page 21, and Table 9); and the effectiveness of the vaccine in treating infected animals in 18 different animal species is provided (Example 3, page 21 and Table 10).

Furthermore, clarification can also be drawn from page 3, lines 5-12 and 20-22 disclosing preferred vaccine combinations in the context of page 4, lines 8-18:

Page 3, lines 5-12:

> This aim has been achieved by using the following fungal strains as vaccinal strains: *Trichophyton verrucosum* (especially No. VKPGF-931/410), *Trichophyton mentagrophytes* (especially No. VKPGF-930/1032), *Trichophyton equinum* (especially No. VKPGF-929/381), *Trichophyton sarkisovii* (especially No. VKPGF-551/68), *Microsporum canis* (especially No. VKPGF-928/1393), *Microsporum canis var. obesum* (especially No. VKPGF-727/1311), *Microsporum canis var. distortum* (especially No. VKPGF-728/120), *Microsporum gypseum* (especially No. VKPGF-729/59). Vaccines can be produced by using various combinations of antigenic material from the above strains together with a suitable carrier.

Page 3, lines 20-22:

> "Another preferred combination of vaccine strains consists of *Trichophyton verrucosum* No. VKPGF-931/410, *Trichophyton mentagrophytes* No. VKPGF-930/1032, *Trichophyton sarkisovii* No. VKPGF-551/68, particularly for use in cattle."

Page 4, lines 8-18:

> In order to prepare a vaccine the following procedure may be used, for example:
>
> Cultures of the strains are homogenized in an aqueous solution containing 0.2 ti 2.0% fermented, hydrolyzed muscle protein (FGM-s), 5 to 12% glucose and 0.1 to 1.2% yeast extract. The concentration of the microconidia is adjusted to 40 to 120 million per milliliter and after 1 to 2 days the mixture is inactivated, *e.g.*, with thiomersal ($C_9H_9O_2SNaHg$) in the ration 1:10,000 to 1:25,000, or with another substance known from the prior art. The resulting suspension is packaged and is ready for use in animals.
>
> The preparation of the vaccines, the dosage to be given and the method of administration for prevention and therapeutic treatment are explained in Examples 1 to 3.

With the before-mentioned extensive guidance provided to the skilled person, Applicants have shown how to make and use both vaccines within the scope of the claims.

Furthermore, the Examiner did not consider and apply the factors and analysis of *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988) and *Ex parte Forman*, 230 U.S.P.Q. 546 (Bd. Pat. App. & Int. 1986). In properly considering and applying the factors concerning enablement, the following factors should be considered: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

With regard to factors (1) and (2), to practice the invention, either 4 or more dermatophytes must be grown, mixed together in a single container, the mixture is inactivated, and the resulting vaccine is bottled (described in the specification on

pages 4, lines 10-18, page 18, lines 15-31), and applied to animals at a dosage and with a route of administration as disclosed in Example 2, page 21, and Table 9 (prevention) as well as Example 3, page 21 and Table 10 (therapy). As set out *supra*, the dosage and route of administration is given for 10 different animal families, and guidance regarding efficacy of the 8-fold vaccine is given for 24 animal species (prevention) and 18 animal species (therapy) all of which represents a very limited amount of routine experimentation under a significant amount of guidance presented in the specification. If at all, there is minimal routine experimentation necessary to test a 4 or more fold vaccine in a similar manner as the 8-fold vaccine. With regard to factor (3), there are several in-depth working examples disclosing the preparation of vaccines according to the invention, the dosage, the route of preventive or therapeutic administration for numerous animal species. With regard to factors (4), (5), (6), and (7), as the nature of the invention is in the immunology, animal health and vaccine art, which is very highly developed, the state of the prior art is high, and the relative skill of those in the art is at a very high level, one would expect one of skill in the art would easily be able to use the directions in the specification to make and use the vaccines according to the invention. Regarding factor (8), it should be pointed out again that the claims presented for review recite specific vaccines consisting of four or more specified dermatophytes.

This situation is in contrast to that of *Ex parte Forman*, where the art was "undeveloped", that at the time (early 1980s) "experiments in genetic engineering produce, at best, unpredictable results", there were no apparent reproducible working examples presented outside the scope of the deposited microorganism strains, nor did there "appear to be … a single detailed example that could be followed by another worker in another lab to obtain a single specific microorganism (vaccine) within Applicants' claims, without recourse to the deposited strains recited in the allowed claims." *Ex parte Forman*, at 548. The instant situation is more like *In re Wands*, where enablement was shown, as Applicants' disclosure, like Wands' disclosure, "provides considerable direction and guidance on how to practice their invention and

presents working examples. There was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known." *In re Wands* at 1406.

35 U.S.C. § 112, first paragraph, certainly does not require each and every embodiment of the invention to be exemplified. Even the lack of a working example (quite contrary to the situation here with several working examples), if all the other factors point to enablement, is not considered to render the invention non-enabled, if one skilled in the art will be able to practice it without an undue amount of experimentation (M.P.E.P. 2164.02; *In re Borkowski*, 164 U.S.P.Q. 642, 645 (CCPA 1970).

Further, the test is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue (M.P.E.P. § 2164.01; *In re Angstadt*, 190 U.S.P.Q. 214, 219 (CCPA 1976); *Atlas Powder Co. v. E.I. DuPont De Nemours & Co.*, U.S.P.Q. 409, 413 (Fed. Cir. 1984). The test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. *The Johns Hopkins University v. Cellpro Inc.* 47 U.S.P.Q.2d 1705, 1719; *PPG Indus., Inc. v. Guardian Indus. Corp.* 37 U.S.P.Q.2d 1618, 1623 (emphasis added).

With the significant amount of guidance presented in the specification, the minimal routine experimentation necessary to test a 4-fold or more vaccine in a similar manner as the 8-fold vaccine can certainly not be considered undue.

Allegation (c)

With regard to allegation (c), Applicants cite Taber's cyclopedic medical dictionary, in existence since 1940 and clearly the standard to the skilled person

(Exhibit A). It is appropriate to compare the meaning of terms given in technical dictionaries in order to ascertain the accepted meaning of a term in the art. *In re Barr*, 170 U.S.P.Q. 330 (CCPA 1971).

"Vaccine" is defined to be used as follows:

> "FUNCTION: Vaccines are used to stimulate **an immune response** in the body by creating antibodies **or** activated T lymphocytes capable of controlling the organism. **The result is protection against disease**; the duration depends on the particular vaccine (emphasis added)."

Therefore, for the use of a vaccine to be enabled, it is fully sufficient to stimulate an immune response which can either be the generation of antibodies or activated T lymphocytes, both requirements do not need to be satisfied. The Examiner's arbitrary requirement of requiring both humoral (antibody-mediated) and cellular (T lymphocyte) responses is neither scientifically justified nor founded in the law. To fulfill the requirements of 35 U.S.C. § 112, first paragraph, it is fully sufficient that the vaccines according to the invention provide an immune response. This is extensively exemplified in Examples 2 and 3, page 21, and Tables 9 and 10 of the specification.

Likewise, the Examiner's arbitrary requirement for an adjuvant to be present in the vaccine is neither scientifically justified nor founded in the law as discussed *infra*. Applicants successfully sell Insol® Dermatophyton and Insol® Trichophyton, presented for review (package inserts presented in Exhibits B and C, respectively). Both vaccines do not require adjuvants due to the superior properties of the vaccine strains contained therein. Thus, it is again respectfully submitted that the subject matter claimed fully complies with the requirements set forth in 35 U.S.C. § 112, first paragraph.

In many of these allegations, the Examiner seems to be attempting to shift the burden to the Applicants to affirmatively prove that Applicants are entitled to a patent, when it is the Examiner's burden to prove that Applicants are not entitled to a patent

with rejections that are supported by evidence and a rational basis. This the Examiner has not done.

Furthermore, Applicants respectfully direct the Examiner's attention to the Declaration of Dr. Igor Polyakov under 37 C.F.R. §1.132 ("the Declaration"). As stated in paragraph 5 of the Declaration, the vaccines of the present invention which are described in the Declaration were prepared essentially according to the method disclosed in the instant application. The minor, insubstantial differences between the method for preparing the vaccines disclosed in the above-identified application and the methods described in the Declaration are described in paragraph 6 of the Declaration. As is stated in paragraph 6 and demonstrated in paragraph 7 of the Declaration, such minor differences had no significant effect on the properties of the vaccines. Further, all of the challenge experiments were performed in the absence of adjuvants (paragraph 5).

Applicants further direct the Examiner's attention to paragraphs 8-12 of the Declaration wherein production and efficacy of dermatomycosis vaccines comprising four and five fungal strains is described. Results of these experiments are presented in Table 1, Examples 2-6. The experiments and results in paragraphs 8-12 correspond to new claims 8, 11, 9, 10, and 14, respectively. Production and efficacy of dermatomycosis vaccines comprising a single fungal strain is described in paragraph 13 of the Declaration; results of these experiments are presented in Table 1, Example 7.

With respect to the declaration, the Examiner states that "in order for a declaration to provide support for enablement of the claimed invention the results/data shown in the declaration have to have been performed by the exact same (i.e. identical) procedure as described in the filed specification." (Office Action page 6). Applicants are not aware of any authority requiring the exact same (i.e identical) procedure. Rather, the guidance of the specification as well as what was well known to one of skill in the art is to be considered.

The experiments described in the Polyakov declaration are supported by whole disclosure of the specification, including any minor differences the experimental design of the Polyakov studies provided with declaration may have with the design of the experiments described in the section "Examples" of the patent application. For example, on page 4, lines 10 to 15 of the specification the conditions for the preparation of the vaccines are described in a general manner: "Cultures of the strains are homogenized in an aqueous solution containing 0.2 ti 2.0% fermented, hydrolyzed muscle protein (FGM-s), 5 to 12% glucose and 0.1 to 1.2% yeast extract. The concentration of the microconidia is adjusted to 4 to 120 million per milliliter and after 1 to 2 days the mixture is inactivated, e.g., with thiomersal (C9H9O2SNaHg) in the ration 1:10,000 to 1:25,000, or with another substance known from the prior art. The resulting suspension is packaged and is ready for use in animals."

Moreover, from page 2, line 15 of the specification it is known, that "Preparations, which are cultivated in agar/wort for 20-25 days at a temperature of 26-28°C." On page 3, lines 28 to 30 of the specification it is mentioned that "Antigenic material for such a purpose can be prepared using methods known from the prior art, e.g., homogenizing the above-mentioned dermatophytes or parts thereof, fractionation of dermatophyte preparations, production of antigenic dermatophyte material by recombinant DNA technology, etc." Altogether, the experiments provided with the Polyakov declaration are made under conditions supported by the specification of the patent application as filed.

Furthermore, the distinctions noted in the Office Action between the Example and the declaration, are only minor differences in experimental parameters that are well within the skill in the art. The MPEP states that "[w]hile care should be taken to compare the steps, material and conditions used in the experiments of the declaration with those disclosed in the application to make sure that they are commensurate in scope; i.e. that the experiments used the guidance in the specification as filed **and what was well known to one of skill in the art**." §2164.05 (emphasis added).

Applicants therefore respectfully submit that the declaration is evidence that must be considered.

Accordingly, Applicants submit that, based on the arguments above, the pending claims comply with 35 U.S.C. § 112, first paragraph, as well as with all other statutory requirements of the U.S. Patent Law. An applicant who complies with the statutory requirements is entitled to a patent. *In re Rouffet*, 47 U.S.P.Q.2d 1453 (Fed. Cir. 1998); *In re Oetiker*, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992); *In re Grabiak*, 226 U.S.P.Q. 870, 873 (Fed. Cir. 1985); *In re Rinehart*, 189 U.S.P.Q. 143, 147 (C.C.P.A. 1976).

Consequently, Applicants respectfully request the Examiner withdrawn the rejection.

Obvious-Type Double Patenting Rejection

Regarding the obvious-type double-patenting rejection, applicants will submit a terminal disclaimer to ensure that any patent issuing on the subject application will have the same term as the '399 patent.

In view of the foregoing it is respectfully submitted that the subject application is in condition for allowance and such favorable action at an early date is earnestly solicited.

Respectfully submitted,

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Date: July 18, 2006

EXHIBIT A

EDITION

18

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CYCLOPEDIC MEDICAL DICTIONARY

F. A. DAVIS COMPANY PHILADELPHIA

Edited by

L. THOMAS, M.D., M.P.H.

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PRINTED IN THE UNITED STATES OF AMERICA

Last digit indicates print number 10 9 8 7 6 5 4 3 2 1

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Library of Congress Cataloging in Publication Data

Taber, Clarence Wilbur, 1870–1968
Taber's Cyclopedic Medical Dictionary, edition 18.

Medicine—Dictionaries I. Thomas, Clayton L., 1921– . II. Title. III. Title: Cyclopedic medical dictionary. [DNLM: 1. Dictionaries, Medical. W 13 T113d 1997 610'.3'21 62-8364
ISSN 1065-1357
ISBN 0-8036-0194-8
ISBN 0-8036-0193-x (indexed)
ISBN 0-8036-0195-6 (deluxe)

V

V **1.** *Vibrio; vision; visual acuity.* **2.** Symbol for the element vanadium.

V̇ **1.** Symbol for gas flow. **2.** Symbol for ventilation.

v L. *vena,* vein; *volt.*

vaccina (văk-sī'nă) Vaccinia.

vaccinable (văk-sĭn'ă-b'l) Capable of being successfully vaccinated.

vaccinal (văk'sĭn-ăl) Rel. to vaccine or to vaccination.

vaccinate (văk'sĭn-āt) [L. *vaccinus,* pert. to cows] To inoculate with vaccine to produce immunity against disease.

vaccination (văk"sĭ-nā'shŭn) [L. *vaccinus,* pert. to cows] **1.** Inoculation with any vaccine or toxoid to establish resistance to a specific infectious disease. SEE: *immunization.* **2.** A scar left on the skin by inoculation of a vaccine.

vaccine (văk'sēn, văk-sēn') [L. *vaccinus,* pert. to cows] A suspension of infectious agents, or some part of them, given for the purpose of establishing resistance to an infectious disease. SEE: table.

Vaccines comprise four general classes:

1. Those containing living attenuated infectious organisms, such as vaccine for poliomyelitis.
2. Those containing infectious agents killed by physical or chemical means, such as vaccines used to protect human beings against typhoid fever, rabies, and whooping cough.
3. Those containing soluble toxins of microorganisms, sometimes used as such, but generally forming toxoids, such as the one used in the prevention of diphtheria and tetanus.
4. Those containing substances extracted from infectious agents, such as capsular polysaccharides extracted from pneumococci.

FUNCTION: Vaccines are used to stimulate an immune response in the body by creating antibodies or activated T lymphocytes capable of controlling the organism. The result is protection against a disease; the duration depends on the particular vaccine. Recovery from measles or diphtheria, for example, usually provides lifelong immunity. The immune system has produced antibodies and memory cells for these pathogens so that subsequent exposure does not result in disease. A successful vaccine does the same thing, usually without risk of illness. The measles vaccine is believed to provide lifelong immunity, but the diphtheria vaccine requires periodic booster doses. More than one type of vaccine may be available for immunization against a specific infectious agent. SEE: *diphtheria; immune response; immunity; immu tion; immunobiologics.*

autogenous v. Bacterial vaccine pared from lesions of the individual inoculated. SYN: *homologous v.*

bacterial v. A suspension of killed tenuated bacteria; used for injectior the body to induce development of a immunity to the same organism.

BCG v. Bacille Calmette-Guéri preparation of a dried, living cultu *Mycobacterium tuberculosis.* In with a high incidence of tuberculosis used in prophylactic vaccination c fants against tuberculosis. It is also in adults who are at high and unavoi risk of becoming infected with tuber sis. A disadvantage of use of this va is that it produces hypersensitivity berculin. As a result, the skin test fc berculin sensitivity becomes positive may persist for 5 years. There is no to distinguish a positive skin test d BCG from one caused by infection *Mycobacterium tuberculosis.*

cholera v. A vaccine prepared killed *Vibrio cholerae.* It is effectiv only a few months.

diphtheria v. SEE: *DPT v.*

DPT v. A combination of diphtheri tetanus toxoids and killed pertussi cilli that is administered intramuscu to immunize children against diphth tetanus, and pertussis.

DTaP v. A preparation of diphtl and tetanus toxoids and acellular pe sis proteins. It may be used for the fc and fifth injections in the series.

Haemophilus influenzae type b vaccine prepared from the bacterial saccharide (HbPV) or polysaccharide verted to protein (HbCV).

hepatitis B v. A vaccine prepared hepatitis B protein antigen produce genetically engineered yeast.

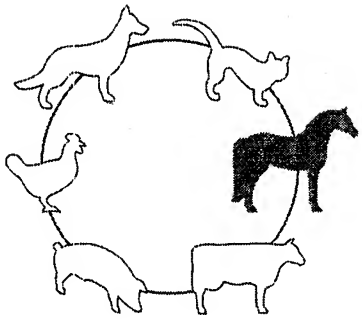
heterologous v. A vaccine derived an organism different from the orga against which the vaccine is used.

homologous v. Autogenous v.

human diploid cell rabies v. A HDCV. An inactivated virus vaccine pared from fixed rabies virus grown i man diploid cell tissue culture.

inactivated poliovirus v. An inject vaccine made from three types of in vated polioviruses. Previously used n poliomyelitis vaccine. SYN: *Salk v.*

influenza virus v. A polyvalent vac containing inactivated antigenic vari of the influenza virus (types A and ther individually or combined) for u areas expected to have epidemics. Its



Insol® Dermatophyton

Inactivated dermatophytosis vaccine

Dermatophytosis is the contagious superficial infection of the skin caused by dermatophytes (ringworm or tinea) and it is the most common skin disease in horses. The spores can survive for years.
Insol(r) Dermatophyton contains highly immunogenic strains of fungus. Based on a special manufacturing process the inactivated microconidia stimulate cell-mediated immune response in particular.
Insol(r) Dermatophyton contains no adjuvants, adsorbents, additives or excipients.

Indications

Active immunisation of horses, dogs, cats, rabbits and guinea pigs against dermatophytosis caused by trichophyton verrucosum, trichophyton mentagrophytes, trichophyton sarkisovii, trichophyton equinum, microsporum canis, microsporum gypseum and for the treatment of animals infected by dermatophytosis caused by these fungal species.

Features

- First vaccine against dermatophytosis in horses
- Covers all relevant strains
- For prophylaxis and therapy
- Easy application / handling

Benefits

- Comfortable way to combat dermatophytosis
- Safe for humans, safe for animals
- Vaccination during incubation possible
- 12 months protection appropriate for long term disease control

Presentation and mode of administration

Available in 5 x 2 ml glass vials for injection
For both prophylactic and therapeutic use 2 intramuscular injections 14 days apart on alternate sides of the body:

- horse ≤400 kg b.w.: 0.3 ml;
  400 - 600 kg b.w.: 0.5 ml; >600 kg b.w.: 0.7 ml
- dogs ≤10 kg b.w.: 0.3 ml; 10 - 40 kg b.w.: 0.5 ml;
  >40 kg b.w.: 1.0 ml
- cats <1 kg b.w.: 0.5 ml; >1 kg b.w.: 1.0 ml
- rabbits <3 kg b.w.: 0.5 ml; >3 kg b.w.: 1.0 ml
- guinea pigs: per 100 g b.w.: 0.1 ml

repeat vaccination at yearly intervals.

Boehringer Ingelheim

Boehringer Ingelheim

Insol® Dermatophyton

Suspension

Für Tiere

Zusammenfassung der Produkteigenschaften

Bei jeder Injektion sollte die Körperseite gewechselt werden.
Zur Aufrechterhaltung des Impfschutzes sollten Wiederholungsbehandlungen nach prophylaktischer bzw. therapeutischer Anwendung in Form von zwei Impfungen im Abstand von 14 Tagen alle 10 bis 12 Monate erfolgen.

5.8 Überdosierung
Eine Überdosierung kann zu einer Verstärkung der aufgeführten Nebenwirkungen führen.

5.9 Besondere Warnhinweise für die Zieltierarten
keine

5.10 Wartezeit
Eßbare Gewebe vom Pferd: 3 Tage

5.11 Besondere Vorsichtsmaßnahmen für Personen bei der Anwendung des Produktes
keine
Im Falle eines versehentlichen Verschütten des Impfstoffes auf die Haut ist diese mit Wasser abzuwaschen.
Versehentliche Selbstinjektion kann zu vorübergehenden Schwellungen an der Injektionsstelle führen. In Fällen schwerer Nebenwirkungen nach versehentlicher Selbstinjektion mit dem Impfstoff sollte ein Arzt aufgesucht werden.

6. Pharmazeutische Daten

6.1 Unverträglichkeiten
Bezüglich möglicher Inkompatibilitäten wurden keine Studien durchgeführt.
Der Impfstoff darf nicht mit anderen Impfstoffen gemischt werden.

6.2 Haltbarkeit
Im ungeöffneten Behältnis:
18 Monate bei einer Lagerung zwischen +2°C bis +8°C
Im geöffneten Behältnis:
14 Tage bei einer Lagerung zwischen +2°C bis +8°C, sofern die Entnahmen ordnungsgemäß erfolgen.

6.3 Hinweise zur Aufbewahrung
Der Impfstoff ist zwischen +2°C und +8°C zu lagern!
Nicht einfrieren! Vor Licht schützen!
Impfstoff für Kinder unzugänglich aufbewahren!

6.4 Behältnis
2 ml-, 5 ml-, oder 10 ml-Glasflaschen der Glasart I, verschlossen mit Bromobutyl-Gummistopfen und Aluminiumbördelkappen

6.5 Zulassungsinhaber
Boehringer Ingelheim
Vetmedica GmbH
55216 Ingelheim

Hersteller
Serumwerk Bernburg
27318 Hoyerhagen

6.6 Besondere Hinweise für die Beseitigung von unbrauchbarem Material
Leere Behälter, nicht völlig aufgebrauchter oder nach Ablauf des Verfalldatums nicht mehr verwendbarer Impfstoff sind unschädlich zu beseitigen.

7. Weitere Informationen

Zulassungs-Nummer: 118a/96

Datum der Genehmigung dieser Zusammenfassung der Produkteigenschaften:
24. 01. 2000

Abgabestatus: Verschreibungspflichtig

Zugelassene Handelsformen:
Packung mit 2 ml
Packung mit 5 x 2 ml

Boehringer Ingelheim Vetmedica GmbH
55216 Ingelheim am Rhein
Telefon 0 18 03 / 60 60 60

Boehringer Ingelheim

21 VDD

1. Name

Insol® Dermatophyton

1. Zusammensetzung

1 ml der inaktivierten Vakzine enthält jeweils mind. $6{,}25 \times 10^{6,0}$ Mikrokonidien der folgenden Pilzstämme:

- Trichophyton verrucosum, Stamm Nr. 410
- Trichophyton mentagrophytes, Stamm Nr. 1032
- Trichophyton sarkisovii, Stamm Nr. 551
- Trichophyton equinum, Stamm Nr. 381
- Mikrosporum canis, Stamm Nr. 1393
- Mikrosporum canis var. distortum, Stamm Nr. 120
- Mikrosporum canis var. obesum, Stamm Nr. 1311
- Mikrosporum gypseum, Stamm Nr. 59

und maximal 0,044 mg Thiomersal in einer Glucose-Fleischextrakt-Suspension

3. Darreichungsform

Suspension zur Injektion

4. Immunologische Eigenschaften

Die Verabreichung des Impfstoffes bewirkt die Ausbildung einer Immunität bei Pferden, Hunden, Katzen, Kaninchen und Meerschweinchen gegen Dermatophytosen, verursacht durch Trichophyton verrucosum, Trichophyton mentagrophytes, Trichophyton sarkisovii, Trichophyton equinum, Mikrosporum canis und Mikrosporum gypseum.

Die im Impfstoff enthaltenen Stämme sind tierischen Ursprungs: Trichophyton verrucosum (Stamm Nr. 410) wurde von einem Rentier, Trichophyton mentagrophytes (Stamm Nr. 1032) von einem Pferd, Trichophyton sarkisovii (Stamm Nr. 551) von einem Kamel, Trichophyton equinum (Stamm Nr. 381) von einem Pferd, Mikrosporum canis (Stamm Nr. 1393) von einer Katze, Mikrosporum canis var. distortum (Stamm Nr.120) von einem Schwarzen Panther, Mikrosporum canis var. obesum (Stamm Nr. 1311) von einem Tiger und Mikrosporum gypseum (Stamm Nr. 59) von einem Pferd isoliert.

Die erzeugte Immunität ist hauptsächlich eine zell-vermittelte Immunantwort und hält in der Regel 10 bis 12 Monate an.

5. Klinische Daten

5.0 Zieltierarten

Pferde, Hunde, Katzen, Kaninchen und Meerschweinchen.

5.1 Anwendungsgebiete

Zur aktiven Immunisierung von Pferden, Hunden, Katzen, Kaninchen und Meerschweinchen gegen Dermatophytosen, verursacht durch Trichophyton verrucosum, Trichophyton mentagrophytes, Trichophyton sarkisovii, Trichophyton equinum, Mikrosporum canis und Mikrosporum gypseum zum Zwecke der Reduktion des Risikos einer klinischen Infektion durch diese Pilzarten, sowie als therapeutische Maßnahme zur Beschleunigung der Abheilung der klinisch sichtbaren Hautveränderungen bei Tieren, die an einer durch diese Pilzarten verursachten Dermatophytose erkrankt sind.

5.2 Gegenanzeigen

Tiere mit Fieber und/oder mit dermatophytosenunabhängigen Symptomen einer infektiösen Erkrankung, sowie Tiere, die unter Kortikoid-Wirkung stehen, sollten nicht geimpft werden.

Jungtiere entsprechend den folgenden Angaben sind von einer Impfung auszuschließen:

Pferde unter 5 Monaten
Hunde unter 6 Wochen
Katzen unter 1 Monat
Kaninchen unter 6 Wochen
Meerschweinchen unter 150 g

Nicht geimpft werden dürfen gestresste Tiere, z.B. Pferde im Auktionsstress.

Insol® Dermatophyton
Zusammenfassung der Produkteigenschaften

5.3 Nebenwirkungen

Nach der Injektion können, besonders bei Pferden, bis zu hühnereigroße Schwellungen an der Injektionsstelle auftreten, die innerhalb von 3 bis 5 Tagen ohne weitere therapeutische Maßnahmen abheilen. In Einzelfällen wurden schmerzhafte, bis zu handflächengroße Schwellungen an der Injektionsstelle in Verbindung mit gestörtem Allgemeinbefinden (z.B. Fieber, Inappetenz, Apathie) beobachtet, die innerhalb von 8 bis 10 Tagen abgeklungen waren. In solchen Fällen ist eine symptomatische Behandlung zu empfehlen, wobei von lokal reizenden Mitteln abgesehen werden sollte.

5.4 Besondere Hinweise für den Gebrauch

Bei Tieren, die sich zum Zeitpunkt der Impfung im Inkubationsstadium befinden, kann es trotz Impfung zum Ausbruch der Erkrankung kommen. Die Hautveränderungen heilen jedoch innerhalb von 2 bis 4 Wochen nach 2. Injektion ab.

Da sich auch im Haarkleid der Tiere Dermatophytose-Erreger befinden können und diese durch die Impfung nicht erreicht werden, ist das Zoonosen-Risiko durch die Impfung zwar deutlich verringert, aber nicht vollständig auszuschließen. Aus diesem Grunde, sowie auch zur Senkung des Infektionsdruckes, ist bei langhaarigen Tieren das Scheren der Haare zu empfehlen. Aus dem gleichen Grunde wird empfohlen, auch solche Tiere zu impfen, die in direktem oder indirektem Kontakt zu infizierten Tieren stehen.

Zur Reduktion des allgemeinen Infektionsdruckes sollten außerdem Reinigungs- und Desinfektionsmaßnahmen der Umgebung sowie der Gebrauchsgegenstände (z.B. Putzzeug) durchgeführt werden.

Erfahrungen aus der Praxis haben gezeigt, dass insbesondere in Edelkatzenbeständen, in denen ein erhöhter Infektionsdruck zu erwarten ist, eine verminderte Wirksamkeit auftreten kann bzw. eine Rezidivneigung beobachtet werden kann.

5.5 Anwendung während Trächtigkeit und Laktation

Aufgrund des Manipulationsstresses stellen Impfungen zu Beginn und gegen Ende der Trächtigkeit allgemein ein Risiko dar und sollten deshalb vermieden werden.

5.6 Wechselwirkungen

Studien zu möglichen Wechselwirkungen wurden nicht durchgeführt.

Es wird jedoch empfohlen, zwischen den Impfungen, sowie innerhalb von 14 Tagen vor und nach den Impfungen keine anderen Immunisierungen vorzunehmen.

5.7 Dosierung und Art der Anwendung

Vor Gebrauch gut schütteln!

Die Impfdosis beträgt für

Pferde:	
unter 400 kg KGW	0,3 ml
400–600 kg KGW	0,5 ml
über 600 kg KGW	0,7 ml
Hunde:	
bis 10 kg KGW	0,3 ml
10 bis 40 kg KGW	0,5 ml
über 40 kg KGW	1,0 ml
Katzen:	
bis 1,0 kg KGW	0,5 ml
über 1,0 kg KGW	1,0 ml
Kaninchen:	
bis 3,0 kg KGW	0,5 ml
über 3,0 kg KGW	1,0 ml
Meerschweinchen:	
pro 100 g KGW	0,1 ml

Sowohl zur Prophylaxe als auch zur Therapie sind 2 intramuskuläre Injektionen im Abstand von 14 Tagen erforderlich.

Ist bei an einer Dermatophytose erkrankten Tieren zwei Wochen nach zweiter Injektion noch keine eindeutige Verbesserung der Haut- und Haardefekte erkennbar, wird eine dritte Injektion empfohlen.

Auf eine strenge intramuskuläre Injektion ist zu achten; eine subkutane Injektion ist unbedingt zu vermeiden.

LM

Insol® Trichophyton

Boehringer Ingelheim

Inactivated trichophytosis vaccine for cattle

Aqueous suspension for intramuscular injection

Composition

1 ml of inactivated vaccine contains:
at least 17 x $10^{6.0}$ microconidia of each of the following strains of fungi:

- Trichophyton verrucosum, strain no. 410
- Trichophyton mentagrophytes, strain no. 1032
- Trichophyton sarkisovii, strain no. 551

and a maximum of 0.040 mg thimerosal
in a glucose meat extract suspension

Indications

Active immunisation of cattle from the age of 1 month onwards against trichophytosis caused by Trichophyton verrucosum, Trichophyton mentagrophytes and/or Trichophyton sarkisovii and as an aid in the treatment of cattle infected by trichophytosis caused by these fungal species.

Contraindications

None.

Undesirable effects

Slight swelling can occur at the injection site (mostly after accidental subcutaneous injection) which clears with no adverse symptoms.
In exceptional cases (ca. 0.05%) shock reactions in the form of dyspnoea, pulmonal oedema, reddish foam around the mouth and nose and heavy transpiration can occur (death can occur in ca. 0.01% of the vaccinated animals). In such cases symptomatic treatment including administration of adrenalin, glucocorticoids and antihistamines, possibly together with a dose of calcium, is indicated.

Special Precautions for use

In the case of animals which are in the incubation phase at the time of vaccination, the disease can still break out in spite of the vaccination. However, the skin lesions heal 2 – 4 weeks after the second injection.

Use during pregnancy and lactation

The vaccination can be carried out at any stage of pregnancy. To date no effect on milk output has been observed.

Interactions

No interaction studies have been performed.

However, it is recommended that no other immunisations be carried out between the vaccinations or within 14 days before and after the vaccinations.

Posology and method of administration

Shake well before use.

The vaccination dose is
for cattle with less than
70 kg bodyweight: 2.5 ml

for cattle with more than
70 kg bodyweight: 5.0 ml

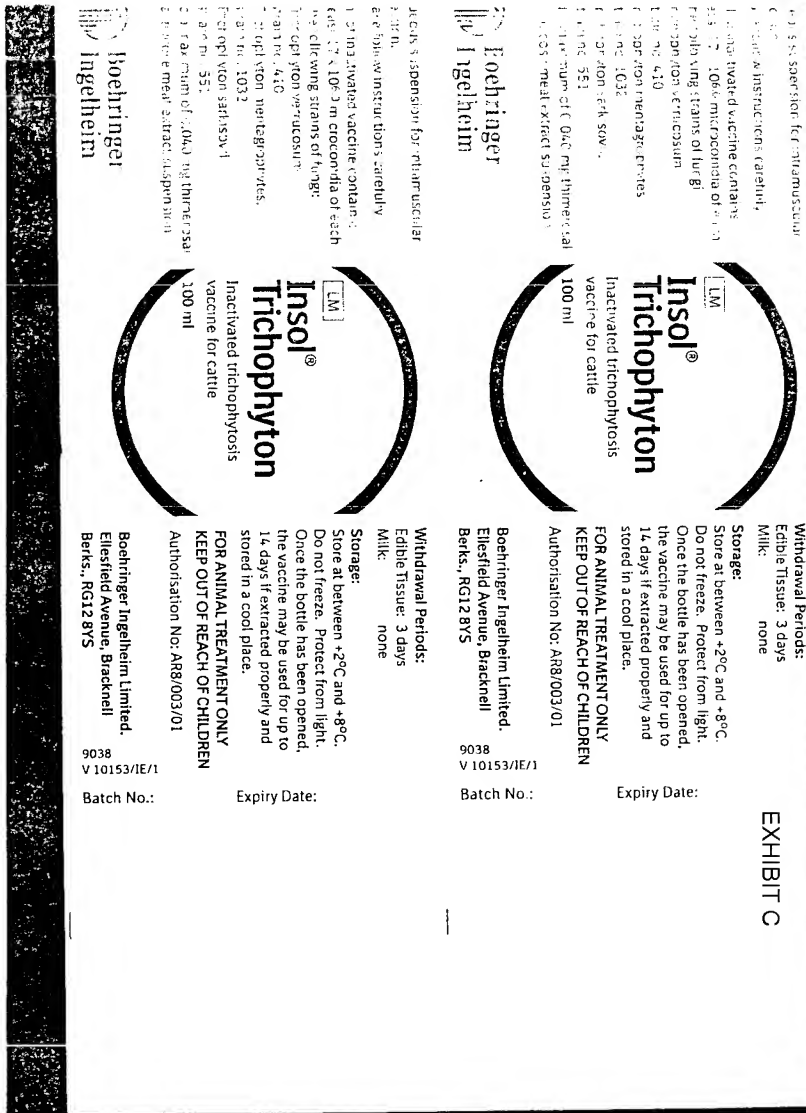


EXHIBIT C

Both for prophylaxis and for therapy 2 intramuscular injections with a 14-day interval are required. The injections should be given on alternate sides of the body. To maintain the vaccine protection after prophylactic or therapeutic administration, repeat vaccinations should be carried out at yearly intervals.

Subcutaneous injection is to be avoided

Overdose
Can lead to slight local intolerance reactions.

Special warnings for the target species
Animals with fever and/or symptoms of an infectious disease other than trichophytosis and animals which are still under the influence of corticosteroids should not be vaccinated. Animals under 4 weeks of age should not be vaccinated. Do not vaccinate stressed animals, for example animals for which a new strawbedding has been freshly prepared.

Withdrawal periods
Edible tissue: 3 days
Milk: none

Special precautions to be taken by the person administering the product to animals
None.

Rinse with water if the vaccine is accidentally spilled onto the skin. Accidental self injection may lead to mild transient swelling at the injection site. In case of severe side effects following an accidental self injection of vaccine a medical surgeon shou d be consulted.

Incompatibilities
No incompatibility studies have been performed.

Storage
Store at between +2°C and +8°C.
Do not freeze. Protect from light.

If stored at between +2°C and +8°C and as long as the vaccine is removed from the vial correctly, the vaccine may be used for up to 14 days after the vial has been opened.

Pack sizes
50 ml, 100 ml or 250 ml glass vials.

Warnings
For animal treatment only.
Keep vaccine out of the reach of children.
Do not use vaccine after the expiry date.
Empty containers and vaccine which is no longer usable after the expiry date are to be disposed of safely according to national requirements.

Manufacturer
Serumwerke Memsen
D-27318 Hoyerhagen
Germany

Authorisation No. AR8/003/01

Boehringer Ingelheim Limited
Ellesfield Avenue
Bracknell, Berkshire
RG12 8YS

V 10154/IE/1

This leaflet was written in March 1998.

9038

Insol®
Trichophyton
Inactivated trichophytosis
vaccine for cattle
100 ml

LM

Insol® Trichophyton

Inactivated trichophytosis vaccine for cattle

100 ml

Withdrawal Periods:

Edible Tissue:	3 days
Milk:	none

Storage:
Store at between +2°C and +8°C. Do not freeze. Protect from light. Once the bottle has been opened, the vaccine may be used for up to 14 days if extracted properly and stored in a cool place.

FOR ANIMAL TREATMENT ONLY
KEEP OUT OF REACH OF CHILDREN

AUTHORISATION NO: AR8/003/01

Boehringer Ingelheim

Boehringer Ingelheim Limited
Ellesfield Avenue, Bracknell
Berks., RG12 8YS

LM

Insol® Trichophyton

Inactivated trichophytosis vaccine for cattle

100 ml

Boehringer Ingelheim

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Batch No.:

Expiry Date:

Aqueous suspension for intramuscular injection.
Please follow instructions carefully.

1 ml of inactivated vaccine contains:
at least $17 \times 10^{6.0}$ microconidia of each of the following strains of fungi:
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